Integrated Medical Model: Bone Fracture Risk Module

GRC Human Research Program Development Team

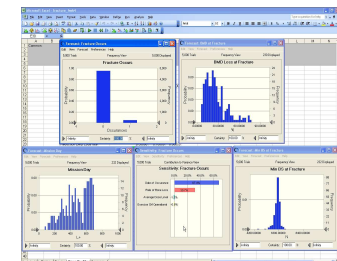|	
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June 5, 2007
Jerry Myers
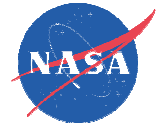
Integrated Medical Model

Potential Medical Condition

Evaluate with IMM

Crew Demographics and Medical history

Treatmetn Options

Training Effectiveness

Best Evidence Clinical Literature

Integrated Medical Model

Equipment and Supplies

Mission Profile

Medical Procedure Effectiveness

Impact to Crew Health

Likelihood of Mission Success
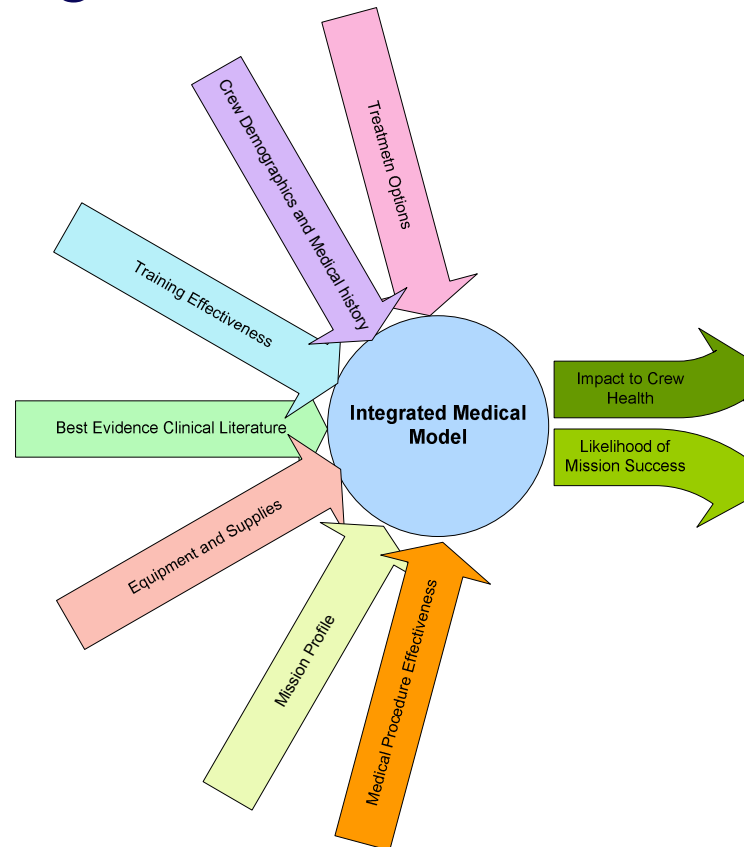
**Likelihood of occurrence, probable severity of occurrence, and optimization of treatment and resources.**

- The Integrated Medical Model (IMM) is a tool for quantifying the probability and consequences of medical risks
- Integrate best evidence in a quantifiable assessment of risk
- Identify medical resources such as skills, equipment, and supplies necessary to optimize mitigation strategies.
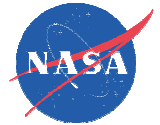
GRC Quantifying Approach and Bone Fracture Risk

- **Observed Early On In the Process**
  - Risk assessment with some medical conditions is confounded by the rigors of space travel
  - Bone Loss, Renal Stones, etc.
- **GRC: Physiological modeling experience makes us uniquely qualified**
  - Develop approaches quantifying the probability of perceived risks where only minimal space-flight data exists.
- **First Focus: Bone fracture in astronauts during exploration missions**
  - Measure of risk based on astronaut bone health and mission parameters
- **Outcome**
  - A set of mission specific probability density functions for fracture at a specific skeletal locations
    - Relate load conditions to the predictions of the bone's structural strength at the time of loading
    - Combine with clinical data on fracture occurrence and an *understanding of the frequency of loading*
    - Produce a quantitative measure of fracture risk
  - Designed to provide input for the ExMC-IMM and the Human Health Risk Assessment Team (HHRAT) PRA analysis

Lumbar Spine

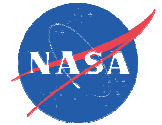**Proximal Femur**
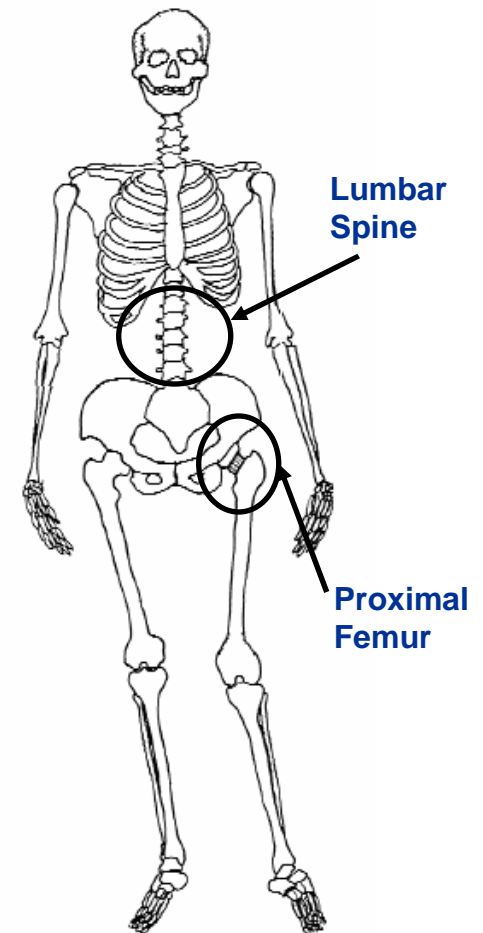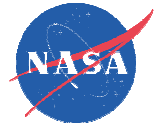
What is a Bone fracture?

Simple Definition:

A Bone Fracture is a structural failure of the bone in response to an applied load

Risk Definition:

Given that astronauts could experience significant skeletal loading during planetary activities, particularly in areas where bone is compromised due to BMD reduction from low-g exposure, there is the possibility of bone fracture leading to astronaut impairment or significant mission impact

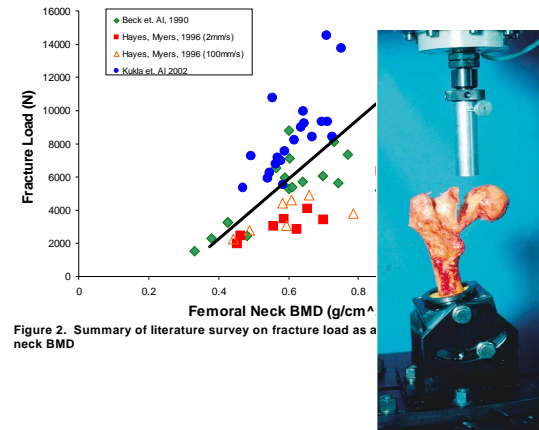# Modeling Fracture Potential For Exploration Missions

courses.washington.edu/me598rc

Figure 2. Summary of literature survey on fracture load as a neck BMD

Biomechanics and Loading
\+
Pre-Flight Health and Bone Loss in Space Flight
\+
Characteristics of Bone Strength

= Estimate of Fracture Probability

- Simulation Model Approach
  - Based on a Monte Carlo sampling of the data space
    - Commercial Simulation Engine: Crystal Ball
    - Integrates best estimate biomedical engineering, clinical and space data
    - Provides for tracking the uncertainty (aletory, epistemic) bounding our output
  - Predicated on estimating a loading event will exceed current bone strength
    - Earth, Moon and Mars Locations
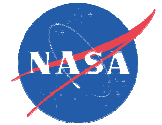
Fracture Metric: Fracture Risk Index
also call the "Factor of Risk"

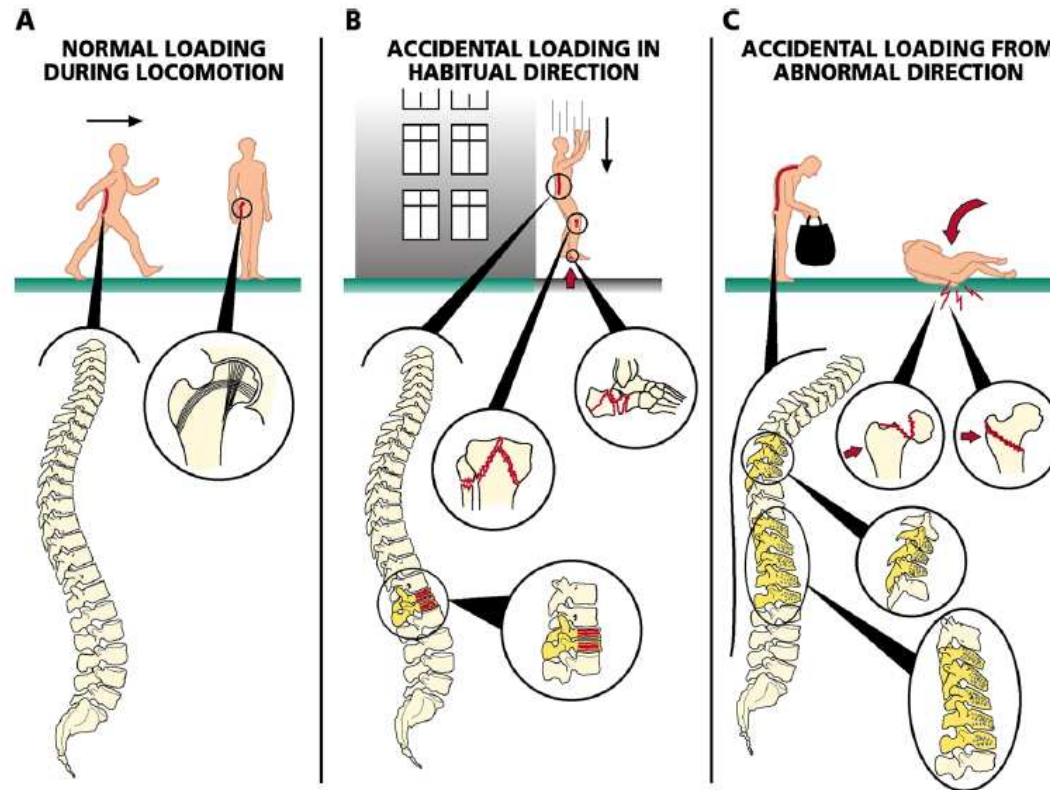$$FRI = \frac{\text{Applied Load}}{\text{Bone Strength}}$$

Hayes WC , Myers ER. Biomechanical considerations of hip
and spine fractures in osteoporotic bone.
Instr Course Lect 1997; 46: 431-38
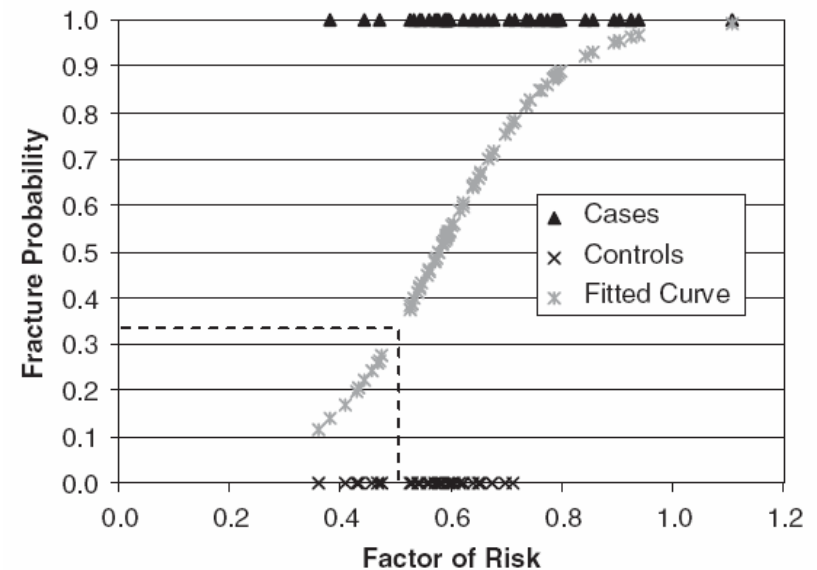
Davidson et al. Prediction of distal radius fracture
in children, using a biomechanical impact model
and case-control data on playground free falls
JBMech 39 (2006) 503–509

- FRI used to track fracture events in several studies
- FRI Converted to Probability of Fracture using Logistic Regression curves
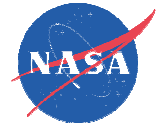
Loading Conditions

A NORMAL LOADING DURING LOCOMOTION

B ACCIDENTAL LOADING IN HABITUAL DIRECTION

C ACCIDENTAL LOADING FROM ABNORMAL DIRECTION

**Stance
Walking
Ladder/Stair
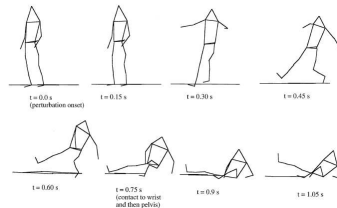   Ascent/Decent**

"Drop Landing"

**Lateral/Posterolateral
Fall Impacting the Hip
Or
Abnormal Lifting**

Calculating Loading in Reduced Gravity Environment

**EVA Suit
Mass & Padding**

Resultant Skeletal Load

Active Response

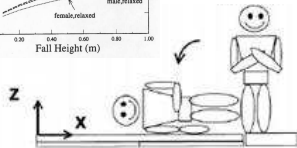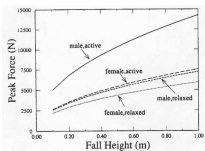**Determine Load Additive or
Attenuation Factors**

**Scale Load to Gravity Level
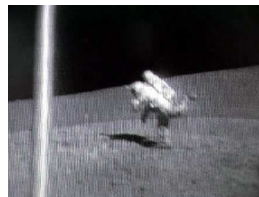Using Appropriate Methods**

$$F = \frac{m\sqrt{2gh}}{\Delta t}$$

$$F_m = F_e \frac{m_m}{m_e} \cdot \left(\frac{\Delta t_m}{\Delta t_e}\right)^{-1} \cdot \left(\frac{g_m}{g_e}\right)^{1/2} \cdot \left(\frac{h_m}{h_e}\right)$$

**Uses the change in momentum
Includes additional mass**

**Estimate of Load
w/ 1g Biomechanics**

**Loading Event Occurs
From Specified
Activity or Incident**

**Represents a perceived loading
state during on surface
activities**

Calculating Bone Ultimate Structural Strength

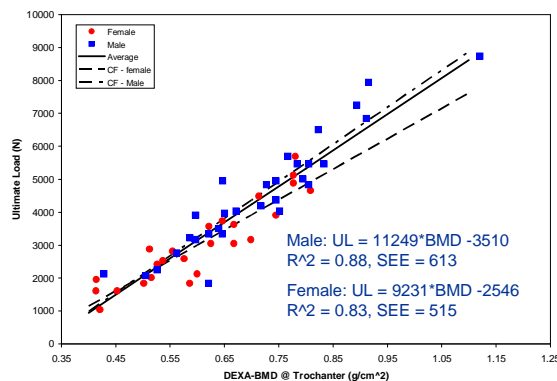**Posterolaterial fall:**
UL Reduced ~0.8% per Degree

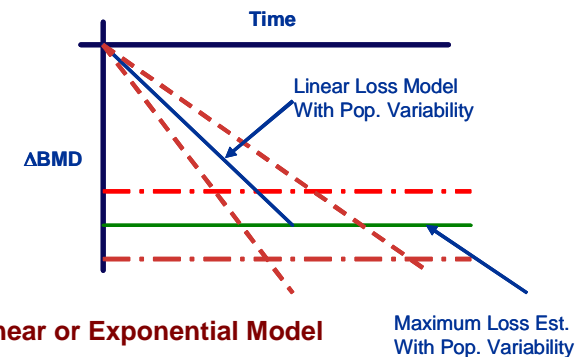*Ultimate Structural Load*
Capacity for Loading Conditions

Apply UL attenuation for
load direction

Male: UL = 11249*BMD -3510
R^2 = 0.88, SEE = 613

Female: UL = 9231*BMD -2546
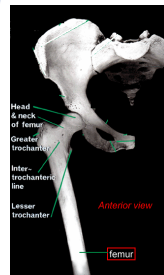R^2 = 0.83, SEE = 515

Use BMD correlations to
Estimate UL

Based on appropriate ex
vivo test data

Estimate Time Course to and Degree
Of Bone Loss at Skeletal Location
On day of loading

Time

Linear Loss Model
With Pop. Variability

ΔBMD

Linear or Exponential Model

Maximum Loss Est.
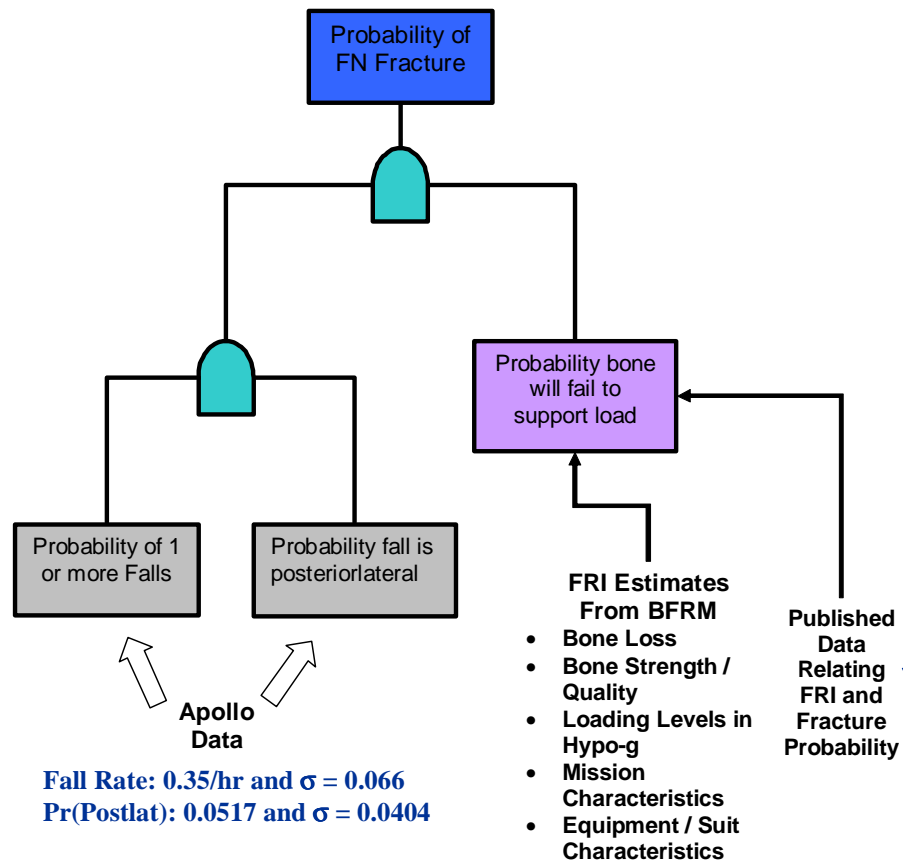With Pop. Variability
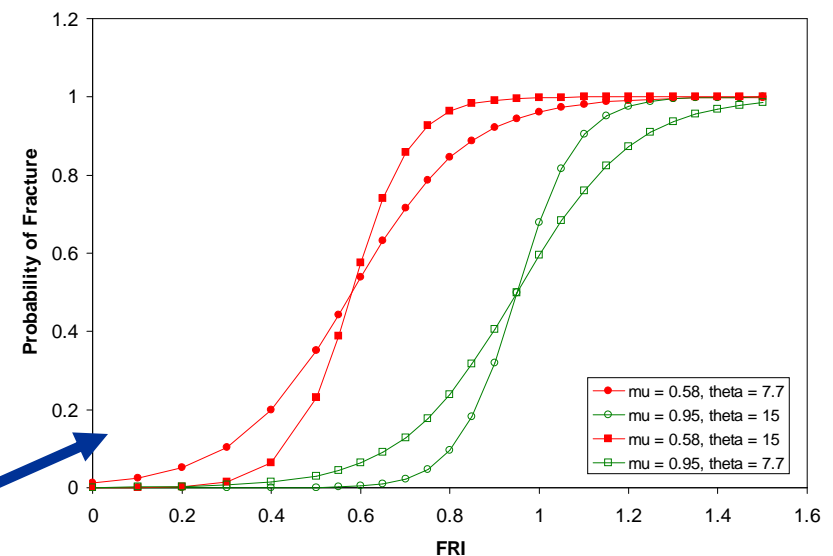
State of Bone at 1g
Pre-Flight DEXA-BMD

NHANES DATA - Represents Pre-
Flight Bone Health, FFD Standards
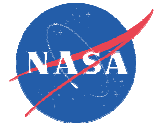**And Reference Max BMD Condition**
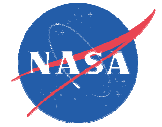
# Tying It All Together: Falls to the Side Impacting Proximal Femur

Probability of FN Fracture

Probability bone will fail to support load

Probability of 1 or more Falls

Probability fall is posteriorlateral

Apollo Data

Fall Rate: 0.35/hr and $\sigma = 0.066$
Pr(Postlat): 0.0517 and $\sigma = 0.0404$

FRI Estimates From BFRM
- **Bone Loss**
- **Bone Strength / Quality**
- **Loading Levels in Hypo-g**
- **Mission Characteristics**
- **Equipment / Suit Characteristics**

Published Data Relating FRI and Fracture Probability

Legend:
- mu = 0.58, theta = 7.7
- mu = 0.95, theta = 15
- mu = 0.58, theta = 15
- mu = 0.95, theta = 7.7

Axis labels: Probability of Fracture (y-axis), FRI (x-axis)

Estimated upper and lower bounds:

**FRI To Probability of Fracture**

Results
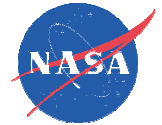
Scenarios and Simulations

- Model Results Averaged Over Reference Mission Simulations
  - Lunar Short: 3 day transient, 8 day surface, 3 day return
  - Lunar Long: 5 day transient, 170 day surface, 5 day return
  - Mars Short: 162 transient, 40 surface, 163 return
  - Mars Long: 189 transient, 540 surface, 189 return
- Male or Female Crew Members
  - Reference Data obtained from LSAH
- EVA or IVA
  - With/Without suit mass and load attenuation models
- For the presented results
  - No attenuation of bone loss due to reduced gravity
  - Modified Linear Loss rates based on LeBlanc
    - Produced the highest values of FRI compared to other loss models
- Focus on
  - Lateral/Posteriolateral fall models
  - Male astronaut on EVA
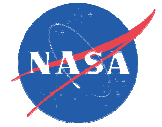 - Other data is available for Female, IVA, and other mission scenarios
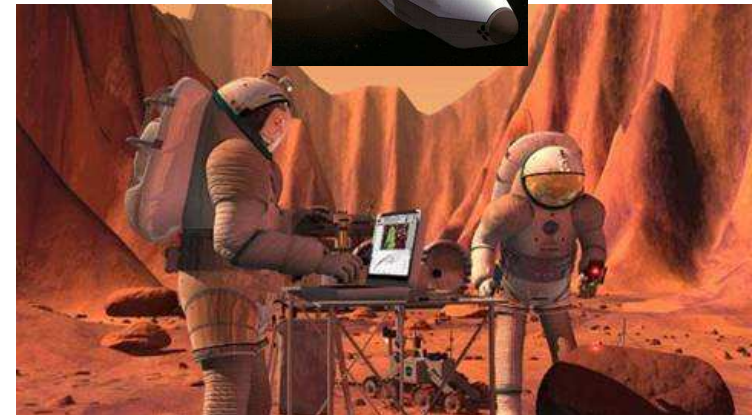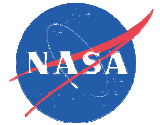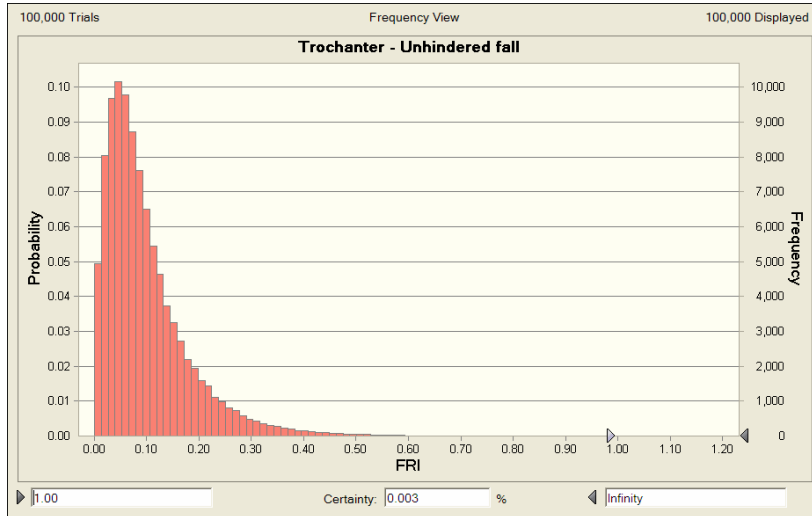
"Smell" Test Validation
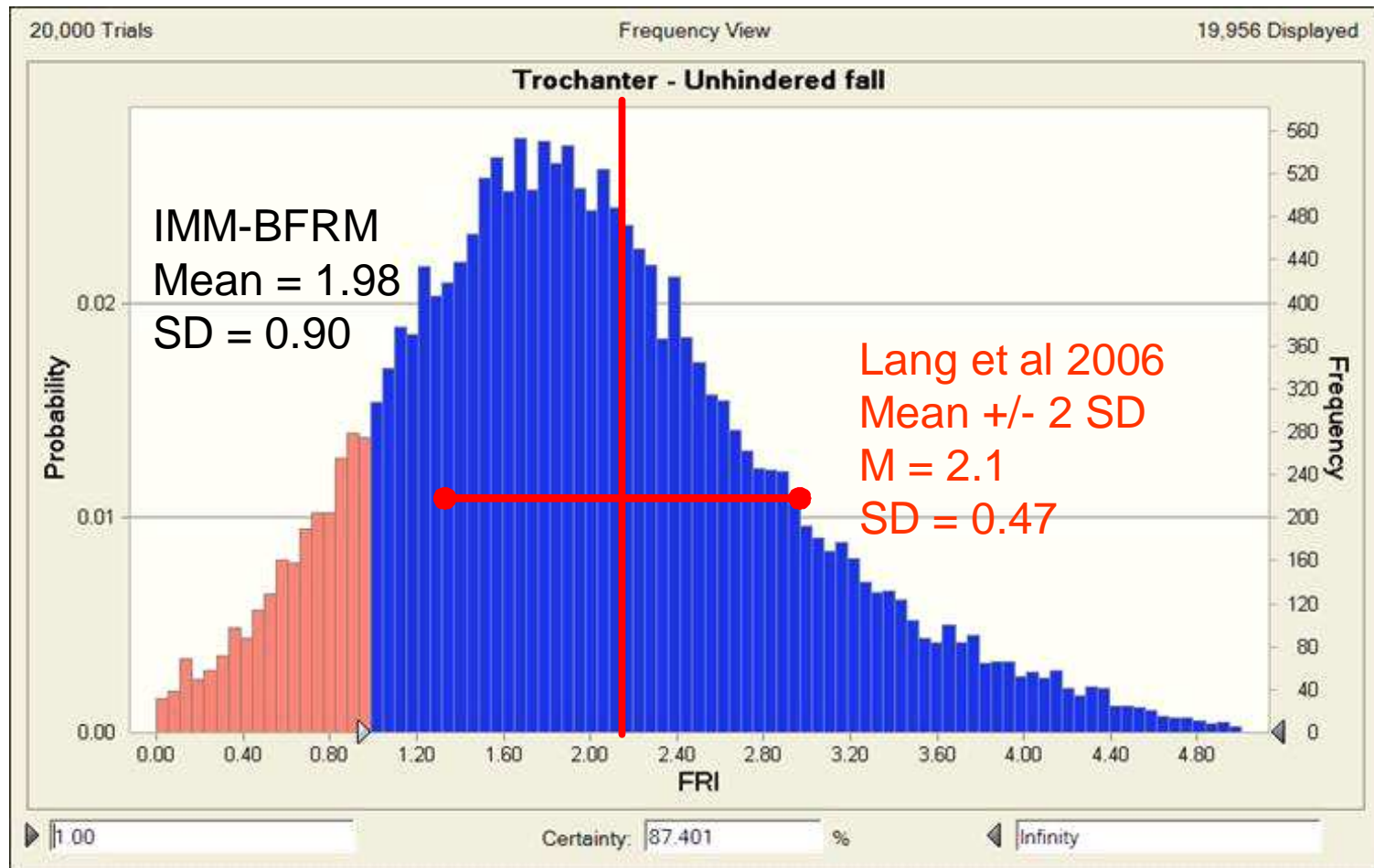
Pre-flight estimate of FRI for Unhindered Posteriolateral Fall
i.e. a fall to the side and slightly backward
Male in 1g with ~1m fall heights

Exploration Mission: Average FRI Estimates
Male on EVA

Lunar: Long

Mars: Long
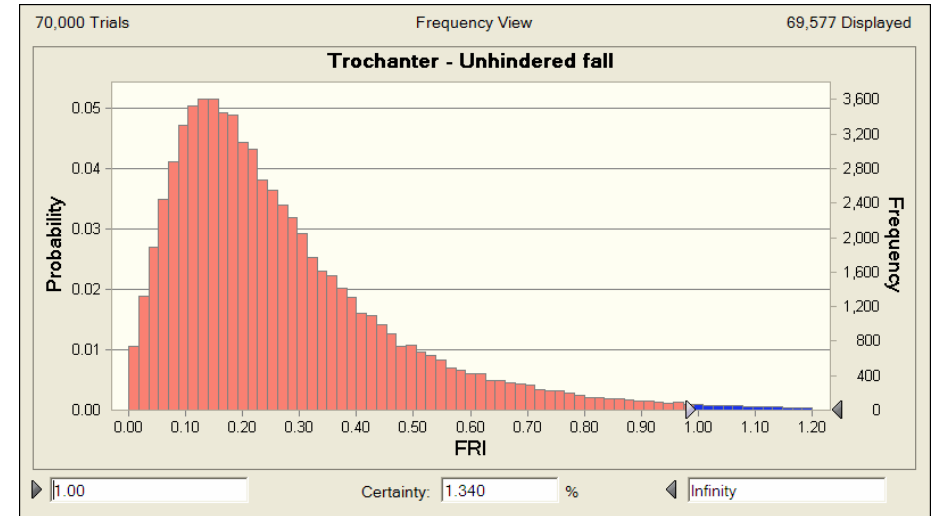
	Lateral Fall		2m Drop Landing		Normal Activity	
	FRI	Cert. >1	FRI	Cert >1	FRI	Cert. >1
L:S	0.09(.07)	<1E-4	0.21(.07)	<1E-4	0.16(.03)	<1E-4
L:L	0.10(.08)	<1E-4	0.22(.07)	<1E-4	0.17(.03)	<1E-4
M:S	0.23(.16)	4.6E-3	0.61(.22)	5.5E-2	0.40(.08)	<1E-4
M:L	0.28(.20)	1.3E-2	0.67(.26)	1.0E-1	0.44(.10)	1E-4

* Note Lateral/Posteriolateral Fall heights range from .25m to ~1m
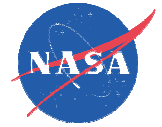
Probability of Fracture
Male on EVA
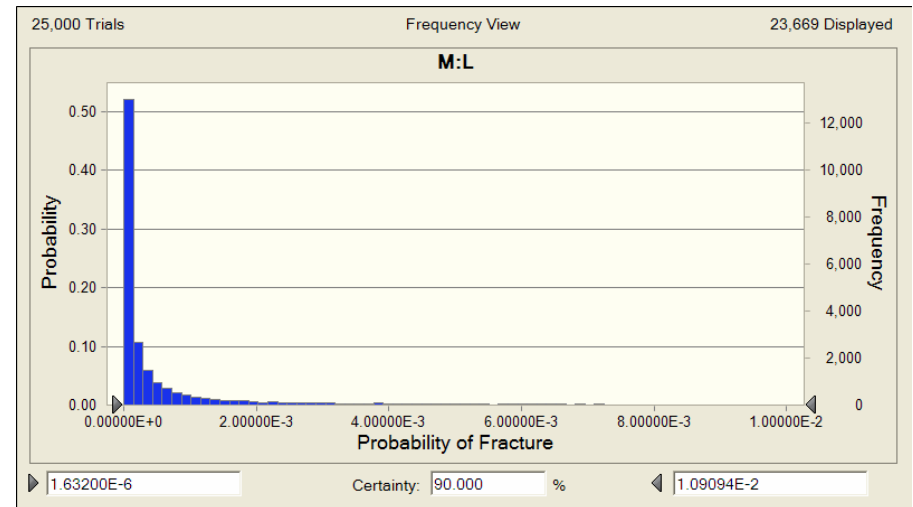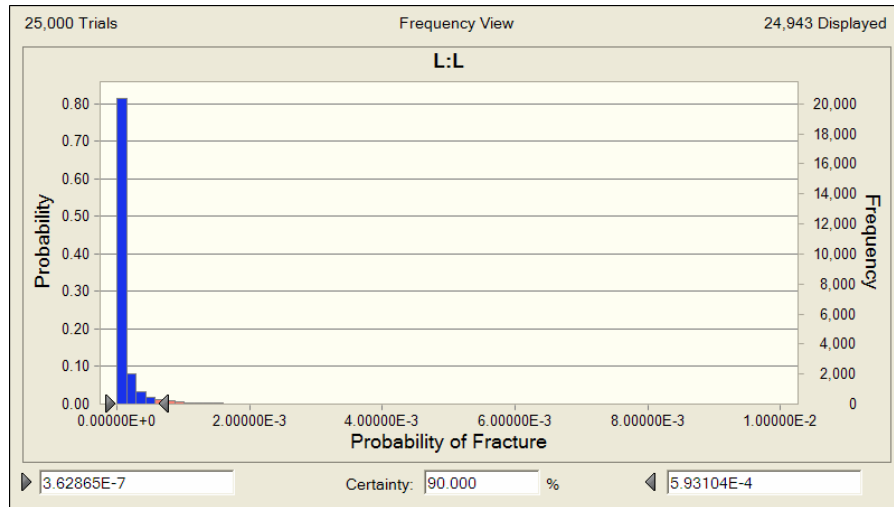
Mission	Fracture Prob	Std	5th Percentile	95th Percentile
Lunar: Short	1.50E-4	1.15E-3	3.30E-07	5.36E-04
Lunar: Long	1.94E-4	1.54E-3	3.47E-07	6.15E-04
Mars: Short	1.44E-3	7.66E-3	1.15E-06	4.85E-03
Mars: Long	2.47E-3	9.95E-3	1.68E-06	1.15E-02
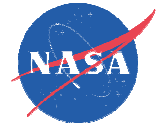
Model Sensitivity

Lunar: Long

100,000 Trials — Contribution to Variance View

Sensitivity: Trochanter - Unhindered fall

Factor	Value
Impact Energy Dissipation Time	43.6%
Suit attenuation during Fal...	28.8%
Successful Attenuation level	-12.3%
Successful reaction	-7.3%
Reference BMD (g/cm^2)	-3.0%
Equivalent Fall Height	2.4%
Fall is posterolateral	0.9%
Varition around LR mean - u...	-0.7%
Astronaut Mass	0.4%

Mars: Long

100,000 Trials — Contribution to Variance View

Sensitivity: Trochanter - Unhindered fall

| Factor	Value
Suit attenuation during Fal...	34.3%
Impact Energy Dissipation Time	27.4%
Successful Attenuation level	-13.8%
Successful reaction	-9.0%
Reference BMD (g/cm^2)	-3.8%
Rate of Bone Loss deltaBMD/...	3.3%
Equivalent Fall Height	2.7%
Date of Occurance	1.7%
Varition around LR mean - u...	-1.6%

- The suit attenuation characteristics and the impulse scaling factors produce the most sensitivity – Represents our Epistemic Uncertainty
- Interesting to note that
  - Successful reaction to the fall is the next most driving factor
  - Bone loss rates are not as significant for lunar missions
  - Reference BMD produces more sensitivity to the calculation than rate of bone loss in both scenarios
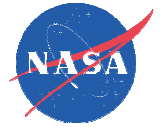
Primary Limitations

- ## Validation with appropriate analog populations

    - ### In process

- ## Loading limited to vulnerable areas

- ## Loading level and type limited in scope

- ## Only DEXA-BMD used to define material strength

    - ### Model assumes equivalence of *ex vivo* and *in vivo* bone strength

- ## Assumption of continued BMD loss on planetary surface has not been validated

- ## Assumption of bone loss plateau may not be representative of ultimate BMD levels

- ## Suit mass and attenuation characteristics need to be better quantified
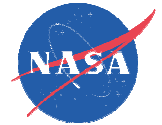
Conclusion

- Provides One of the First Methods for Quantifying Fracture Risk
  - Includes models of loading as well as bone strength related to astronaut activity and health
  - Results agree with more targeted methods used in pre-flight evaluation
  - Illustrates GRC's unique capabilities can be used to address estimates of medical risks
- Integrative approach accounting for extenuating factors
  - Equipment - EVA suit parameters
  - Vehicle – Egress ladder and storage
  - Bone Health – Relating loss to bone strength decrement
  - Training and Operations – Frequency of loading events
- Can be easily used to generate "what if" scenarios
  - What if reduced gravity is osteo-protective?
  - What if the FFD is reduced to t-score of -1.25?
- Can easily incorporate new data as it becomes available
  - Modular and follows object oriented programming practices
- Currents efforts
  - Proximal Femur (Completed - Documentation by June 2007)
  - Lumbar Spine Fractures (June 2007)
  - Radial Arm Fractures (August 2007)
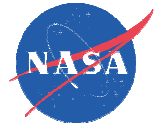
Continuing Work With IMM, HHRAT

- For Bone:
  - Actual Suit Characteristics (attenuation, etc.)**
  - Effects of Exercise Stimulus and Planetary Activities on Bone Health
  - Clinical Measures and Bone Loss Markers
- New Topic Areas
  - Renal Stones Occurrence Module
  - Behavioral Health and Performance Module
  - Interactions between Risk Conditions for Existing Modules
  - Additional Modules
    - Consultation with program management office
    - Houston trip tomorrow
- Looking to expand
  - If interested let us know
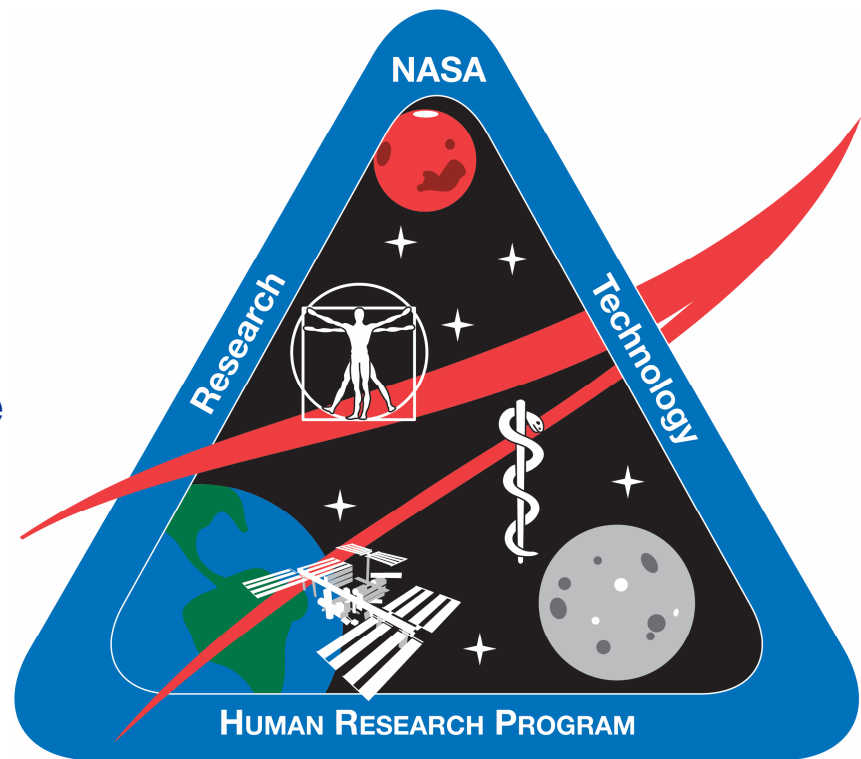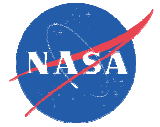
Special Thanks for Their Guidance

- NASA
  - IMM Project Team
    - Doug Butler
    - Kieran Smart
  - ExMC Project Team
  - Bone Lab
    - Jean Sibonga
  - Members of the ESPS working group
  - HH Risk Assessment Team
    - John Charles
    - Michelle Edwards
  - HRP Management

- NSBRI – Bone Loss Team
  - Peter Cavanagh
  - Tom Lang
  - Joyce Keyak
  - Ted Bateman

- And through these, many other helpful contacts